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Case Report

A pediatric case of cat scratch disease, complicated by meningitis, diagnosed by metagenomic next-generation sequencing

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ABSTRACT

Background. Cat scratch disease (CSD) presents with diverse symptoms; however, meningitis as a complication is rare, and effective treatment strategies remain underexplored.

Case Presentation. An 11-year-old girl presented with a prolonged fever of unknown origin, mild cough, and headache. Metagenomic next-generation sequencing (mNGS) identified *Bartonella henselae* in the bloodstream, and cerebrospinal fluid analysis confirmed meningitis. The patient was diagnosed with CSD complicated by meningitis and demonstrated a successful recovery following treatment with doxycycline, rifampicin, and prednisone.

Conclusions. In CSD patients presenting with headaches and persistent fever, the possibility of meningitis should be considered. mNGS is a valuable diagnostic tool for CSD, especially in cases of fever of unknown origin. The combination of doxycycline, rifampicin, and prednisone proved effective in managing CSD with meningitis.

Key words: cat scratch disease, *Bartonella henselae*, meningitis, pediatric, metagenomic next-generation sequencing.

Cat scratch disease (CSD), a zoonotic bacterial infection mainly caused by *Bartonella henselae (B. henselae)*, exhibits a global prevalence. CSD is characterised by fever, erythematous papules at the site of scratches or bites, and regional lymphadenopathy.[1] Atypical manifestations may involve various organs, including the eyes, nervous system, heart, liver, spleen, musculoskeletal system or present as prolonged fever of unknown origin.[2,3] The primary neurological manifestations of CSD include neuroretinitis, encephalopathy, spinal radiculitis, and cerebellar ataxia.[4,5] Nonetheless, meningitis remains a rare occurrence in CSD patients.[5]

Metagenomic next-generation sequencing (mNGS) has emerged as a valuable tool in clinical infectious disease diagnosis, enabling rapid and accurate identification of multiple pathogens from diverse sources.[6] Here, we report a pediatric case of CSD complicated by meningitis diagnosed using mNGS. This case highlights the importance of considering meningitis in CSD patients and underscores the role of mNGS in diagnosing CSD, particularly in cases of fever of unknown origin.

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Case presentation

An 11-year-old girl developed a fever 15 days before admission to our hospital. The patient's personal and family histories were unremarkable, and he had no history of prior blood transfusions.

Initially, the patient experienced a low-grade fever, which gradually escalated to a high fever of 40°C, occurring four times daily, accompanied by a slight cough and headache. The physical examination revealed no abnormalities at a local hospital. A routine blood test revealed elevated white blood cell counts (WBC: 11.53 × 10^9/L, normal range: 4–10 × 10^9/L) and C-reactive protein levels (CRP: 18.4 mg/L, normal range: < 0.5 mg/L). The chest computed tomography scan revealed small patchy opacities in the right upper lobe and bilateral lower lobes, most suggestive of chronic inflammation, along with a ground-glass opacity nodule in the posterior segment of the right lower lobe. After treatment with oral cough medication, a four-day course of oral cefdinir, and subsequent intravenous piperacillin-tazobactam (112.5 mg/kg every 8 hours) for four days, the patient's cough improved. However, due to persistent fever, she was referred to our hospital for further evaluation.

Upon admission, physical examination revealed no positive signs. The patient was alert, with no meningeal signs or pathological reflexes. Blood tests showed a normal white blood cell count (10.5 × 10^9/L) but elevated CRP levels (36.4 mg/L). The erythrocyte sedimentation rate was significantly increased at 68 mm/hour (normal range: <26 mm/hour). Comprehensive laboratory investigations, including renal and hepatic function tests, ferritin levels, serological testing for Epstein-Barr virus and cytomegalovirus, assessment of cellular and humoral immunity, rheumatoid factor, antinuclear antibodies, anti-mitochondrial antibodies, and bone marrow aspiration with culture, all yielded normal results. Cardiac evaluation via echocardiography and immunological screening with purified protein derivative and interferon-gamma release assay were unremarkable. The respiratory multiplex nucleic acid test was negative, including influenza virus, parainfluenza virus, adenovirus, rhinovirus, coronavirus. Imaging studies, including chest computed tomography and cranial magnetic resonance imaging, revealed no structural or pathological abnormalities.

Diagnosis and treatment

The patient was initially diagnosed with fever of unknown origin and acute bronchitis. Despite receiving six days of intravenous cefoperazone sodium and sulbactam sodium (50 mg/kg every 8 hours), along with oral azithromycin (10 mg/kg once daily for the first day, followed by 5 mg/kg once daily for the next 4 days), the fever persisted. Additionally, her headaches worsened, particularly during febrile episodes, with no abnormalities on neurological examination. Subsequent cerebrospinal fluid (CSF) analysis revealed an elevated nucleated cell count (50×10^6/L; reference range <15×10^6/L) with lymphocytic predominance (78%), while biochemical parameters were within normal limits. However, broad-spectrum quantitative PCR assays targeting 23 bacterial and viral pathogens (including herpes simplex virus types 1 and 2, but excluding *B. henselae*) returned negative results.

Suspecting meningitis associated with viral or atypical bacterial infection, the therapy was adjusted to intravenous acyclovir (10 mg/kg every 8 hours), ceftriaxone (50 mg/kg every 12 hours), and vancomycin (15 mg/kg every 6 hours), considering the possibility of methicillin-resistant *Staphylococcus aureus* infection. However, the fever persisted. Consequently, a blood sample was collected for pathogen detection via mNGS, using an Illumina NextSeq 550 sequencer with a single-end 75-base-pair sequencing strategy. A total of 36,744 reads were ultimately analyzed, revealing four specific sequences corresponding to *Bartonella henselae*. The patient also reported a history of

a cat scratch on her left wrist two months prior, which had not been treated.

CSD complicated by meningitis was considered. The treatment regimen was modified to oral doxycycline (2.2 mg/kg every 12 hours) and rifampin (10 mg/kg every 12 hours). By the second day, the patient's temperature had normalized (36.5–36.8 °C), and the headache had alleviated. Prednisone (1 mg/kg) was initiated three days later. Blood tests, CRP levels, and biochemical markers returned to normal ranges after one week of treatment. The patient received six weeks of rifampin and doxycycline therapy in total. Concurrently, the prednisone dosage was gradually tapered over one month. During follow-up interviews conducted by phone at one and three months post-discharge, the patient reported no discomfort or adverse symptoms.

Written informed consent was obtained from the parents for this publication.

Discussion

CSD is the primary clinical manifestation of *B. henselae* infection, most commonly transmitted through percutaneous inoculation via scratches, bites, or contact with flea-infested cats. While CSD symptoms vary, meningitis as a complication is exceedingly rare.[7] In this case, the child presented with a prolonged fever of unknown origin and headaches. CSF analysis confirmed meningitis. Subsequent detection of *B. henselae* in the blood and targeted antibiotic therapy led to resolution of the fever and headaches, clinically supporting the association between meningitis and *B. henselae* infection. However, the absence of CSF mNGS testing precluded differentiation between bacterial and aseptic meningitis.

CSD is typically diagnosed clinically and confirmed serologically, with cat contact or scratches serving as important diagnostic clues. Immunofluorescence antibody tests and enzyme immunoassays are commonly used for detecting *B. henselae* antibodies, although their specificity and sensitivity vary.[8] *B. henselae* culture is challenging due to its facultative and fastidious growth characteristics. PCR assays, while highly specific, exhibit variable clinical sensitivity and are costly, limiting their availability to specialized laboratories.[9] mNGS has been applied in diagnosing CSD.[10] As a rapid and unbiased diagnostic methodology, mNGS enables researchers to explore pathogen-related inquiries without inherent biases. It facilitates earlier diagnosis and initiation of targeted antibiotic therapy by simultaneously and promptly detecting multiple pathogens, particularly beneficial for identifying rare, atypical, and complex infectious diseases.[11] However, mNGS is relatively expensive and less effective for determining drug resistance, with a high risk of microbial contamination during testing. Additionally, interpreting mNGS results also poses challenges.[12]

Therapies of CSD are tailored according to the severity of clinical symptoms. Typical or milder cases of CSD are often self-limited and resolve spontaneously within 2–4 months.[3] However, severe forms of CSD necessitated therapeutic intervention.[13] Therapies for complicated CSD mainly consist of azithromycin, rifampin, ciprofloxacin, trimethoprim/sulfamethoxazole, and/or gentamicin, either as monotherapy or in combination. However, guidelines for paediatric patients or no standardized treatment protocols for CSD complicated by meningitis are limited. However, a regimen of doxycycline and rifampin was suggested for children older than eight years, administered for a duration of 4–6 weeks.[14] Additionally, oral prednisone for six weeks was suspected to be beneficial in cases involving neurological manifestations or severe complications.[14-16] Despite receiving five days of azithromycin in the initial phase, the patient in this case exhibited no improvements, which may be related to the severity of CSD characterized by prolonged fever and meningitis. However, the patient responded well to a regimen of doxycycline, rifampin, and

oral prednisone, confirming the diagnosis and effectiveness of the treatment strategy.

Conclusions

In patients with CSD presenting with headaches and persistant fever, consideration of meningitis is crucial. mNGS proves beneficial for diagnosing CSD, particularly in cases of fever of unknown origin, facilitating accurate diagnosis and prompt initiation of treatment.

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Ethical approval

Publication of this case report followed the regulations of Hospital and was conducted according to the latest version of the Helsinki Declaration. Written informed consent for publication was obtained from the patient's guardian. All identifiable patient information was omitted during the manuscript's development.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: LJ, YL; data collection: YL; analysis and interpretation of results: LJ, YL, YW; draft manuscript preparation: LJ, YL. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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